Workshop 3:Prevention for Women without Prenatal Care (Rapid HIV Testing)

Moderator: Marc Bulterys

Perinatal HIV Rapid Testing: Medical Center of Louisiana

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Denise Foxworth presented.

Perinatal HIV transmission rates in Louisiana have declined from around 25% in 1993 to about 5% in 1998 (latest published data). ZDV use in HIV-positive women giving birth in Louisiana increased from around 50% in 1993 to nearly 90% in 1999.

Administrative Region 1 of the State Department of Health and Hospitals includes the city of New Orleans. In this region, ZDV use in HIV-positive women giving birth increased from below 50% in 1993 to a high of more than 90% in 1998, but then decreased to near 80% in 1999. This decrease was accompanied by an increase in the number of babies born to HIV-infected mothers.

There are two HIV screening programs at the Medical Center of Louisiana at New Orleans. An ambulatory obstetric clinic screening program has an acceptance-of-testing rate of more than 99%. A total of 2,864 voluntary HIV screening tests revealed a seroprevalence in this population of 1.7%. Screening is also a part of inpatient obstetric services , which manage 3500-4000 deliveries annually; 10%-15% of women who present for delivery have had no prenatal care.

The Single Use Diagnostic System for HIV-1 (SUDS, Murex Corporation) is the only test approved by the Food and Drug Administration (FDA) for use in the United States. Our initial experience with SUDS testing revealed the following:

- 20% of HIV-exposed births were identified with SUDS tests in the first 7 months of screening
- 63% of SUDS+ women diagnosed during labor received intrapartum ZDV
- seroprevalence among women delivering with inadequate prenatal care was 4.8%
- SUDS positive predictive value was 100% when testing intrapartum women with inadequate care.

In 1999, 703 women were screened with the SUDS test. Sixteen of 22 positive SUDS tests were confirmed by EIA and Western Blot. HIV seroprevalence was 2.3% among SUDS-tested pregnant women. Sensitivity/specificity of the test was 100% / 99.1%. Positive predictive value was 73%; negative predictive value was 100%.

In 2000, 1075 SUDS tests were performed. Ten of 16 positive SUDS tests were confirmed by EIA and Western Blot. HIV seroprevalence was 0.9% among SUDS-tested pregnant women. Sensitivity/specificity of the test was 100% /99.4%. Positive predictive value was 62.5%; negative predictive value was 100%.

In 1999, the monthly total of SUDS tests administered ranged from lows of 27 and 28 in February and October to a high of 151 in December, nearly twice as many as the previous high months of August (79) and September (78). In 2000, the monthly high was 133 in January. Number of tests remained fairly high through August when 123 tests were administered, then showed a steady decline to a low of 33 tests in December. Monthly totals of positive SUDS tests did not vary much (0–3) over the 2-year period.

A 6-month period (February–July) was reviewed to determine time to test completion. Median time for this 6-month period ranged from 79 to 105 minutes. During this same period the percentage of tests completed in less than one hour ranged from 24.1% to 39.7%; the percentage completed in less than 2 hours ranged from 70.3% to 83.6%.

To summarize our experience:

- SUDS tests demonstrate an adequate positive predictive value when employed in high seroprevalence obstetric settings.
- The efficacy of obstetric rapid testing appears greatest when applied to intrapartum patients with inadequate prenatal care in high seroprevalence populations.
- When appropriate rapid assays are available, the development of point-of-care testing will reduce delays in test reporting.

The Connecticut Experience

Susan Barringer, School of Nursing, Yale University School of Medicine

We decided to examine the use of two different methods of HIV testing in the perinatal period for women who have not been tested earlier in pregnancy: "expedited" ELISA and SUDS. Initiation of AZT therapy even within the first 48 hours of life may decrease the rate of transmission. Cesarean section can further reduce the risk of transmission.

SUDS is the only FDA-approved rapid HIV test. It has a false positive rate of about 1% (similar to ELISA). To make effective use of SUDS, a laboratory technician was on call 16 hours a day. Results were phoned to the clinician and confirmed by ELISA (and, if positive, by Western Blot).

For the ELISA test, a specimen was collected from the mother, cord blood (or baby). Counseling and testing were done at the most appropriate time. Tests were run at 6:30 a.m., 6 days a week. ELISA results were reported to the clinician (later confirmed with Western Blot, if positive).

Two large urban hospitals in Connecticut were selected for the study, which ran from January to August 2000. Eligible subjects were women who had not been tested earlier in pregnancy. Data were collected on demographic characteristics of the study participants, and on date and time of a) admission to the hospital, b) rupture of membranes, c) birth of the infant, and d) when the HIV result was available.

During the study period, Hospital "A" conducted 56 ELISA tests and 17 SUDS tests; Hospital "B" conducted 6 ELISA tests and 40 SUDS tests. About one-third of the study population were African American, one-third were White, and one-fifth were Hispanic. Ten (8.4%) of the 119 patients had a history of drug use; 7 (5.9%) had an STD during pregnancy; 28 (23.5%) had inadequate prenatal care;

and a total of 37 (31.1%) had some risk factor for HIV infection.

A preliminary analysis of the timing of the availability of results includes very large standard deviations because the testing occurred in a number of atypical labor and delivery situations; further analysis is needed to refine these numbers. However, this preliminary analysis indicated that mean time to availability of test results for the ELISA was 30.5 hours (SD=17.3) from hospital admission, 28.9 hours (SD=19.96) from rupture of membranes, and 24.5 hours (SD=17.5) from birth of the child. Mean time to availability of test results for the SUDS was 11.1 hours (SD=26.5) from hospital admission, 6.5 hours (SD=26.6) from rupture of membranes, and 6.5 hours (SD=51.1) from birth of the child.

The proportion of results available before rupture of membranes was 0 for ELISA and 22.4% for SUDS; before the birth of the child was 6.5% for ELISA and 41.1% for SUDS; and within 48 hours of birth was 91.9% for ELISA and 96.4% for SUDS.

All 62 ELISA tests were negative; 54 of the 57 SUDS tests were negative, 2 were true positives, and 1 was a false positive.

We have drawn the following conclusions from our study:

- Women who had a SUDS test were more likely to receive their test result before rupture of membrane and before the birth of the child.
- There was not a significant difference between the SUDS and ELISA tests in receiving test results within 48 hours of delivery.
- Most women who had no prenatal test or who had risk factors were able to receive HIV test results within 48 hours of the birth of the child.

Therefore, using a rapid HIV test for women in the labor and delivery setting allows for "early" initiation of antiretroviral therapy to prevent mother-to-child transmission of HIV. Use of a rapid HIV test or expedited ELISA testing in the setting of labor and delivery will also allow most women who need testing to have a result within 48 hours of birth, which is the time period in which antiretroviral therapy must be initiated.

Overview of the MIRIAD Project

Marc Bulterys, Division of HIV/AIDS–Surveillance and Epidemiology, Centers for Disease Control and Prevention

The objectives of the Mother Infant Rapid Intervention At Delivery (MIRIAD) project are to:

- evaluate innovative approaches to counseling and voluntary rapid HIV testing for women in labor with unknown HIV status
- assess feasibility of obtaining informed consent during labor or soon after birth
- describe barriers to HIV testing and reasons for lack of prenatal care
- assess rapid delivery of ARV prophylaxis to late presenters
- evaluate neonatal therapy adherence; and receipt of post-natal care for women identified as HIV-infected.

The MIRIAD project is limited to institutions with relatively high HIV prevalence (0.8% - 4%) among childbearing women. There are five primary sites in Atlanta, Chicago, Miami, New Orleans, and New York City. Funding was awarded for 4 years; the project began in October 1999. The first year was devoted to protocol development and piloting; in the second and third years, the project will be expanded to other hospitals in the same geographic area. Project sites will link collaboratively with PACTG protocols.

The biomedical research priorities of MIRIAD include:

- evaluation of rapid HIV testing algorithms
- infant blood specimens to be collected—cord, neonatal, 2 weeks, 4 weeks, 6 weeks, 3 months, and 6 months
- virologic sub-studies (e.g., nasal/oral suction material for PCR detection of HIV)
- assess ART resistance among drug-naïve HIV-positive women and among infected infants
- mechanism of action of AZT and NVP prophylaxis
- adherence to neonatal therapy
- host-related genetic factors and HIV transmission.

The behavioral research issues are to:

- assess feasibility of informed consent during labor; and retention post-delivery
- determine reasons/barriers for lack of prenatal care
- measure perceived social support and psychosocial assets in mothers
- determine factors predicting foster care referral
- describe patterns of adherence to ART in women and their children
- evaluate an intervention to improve adherence to neonatal prophylaxis through a modified directly observed therapy.

At each site, a minimum of 1000 women presenting with unknown HIV status late in pregnancy will be screened using two rapid HIV assays (6000 – 8000 / year across sites). We expect each site will identify and enroll approximately 20 – 30 HIV-1 infected women into the MIRIAD rapid intervention protocol and mother-infant follow-up (a total of 100 – 140 / year across sites). Three subgroups of HIV-positive women and their infants will be enrolled into the MIRIAD intervention protocol: a) women presenting in labor, b) late-registrant mothers $\geq$34 weeks of gestational age, and c) women identified with primary HIV infection.

Informed Consent Issues in MIRIAD

Denise J. Jamieson, Division of HIV/AIDS Prevention–Surveillance and Epidemiology, Centers for Disease Control and Prevention

We have faced several major challenges in obtaining informed consent from pregnant women for participation in the MIRIAD project. These challenges include:

- substantial proportion of women are recruited in labor (peripartum group 70%)
- many women had no prior prenatal care
- there is no established relationship with provider or health care system to build on

- the target population is particularly vulnerable to negative consequences of a positive test
- labor itself is physically and emotionally demanding
- focus of the woman is on anticipated delivery, alleviation of pain
- circumstances of labor amplify difficulties of pretest and post-test counseling.

A major aim of MIRIAD is to determine the feasibility and acceptance of informed consent from the women for rapid testing and evaluate the informed consent process in order to develop a more effective and efficient method for approaching women in labor and delivery. Development of this more effective and efficient method has been approached in four ways: preliminary focus groups, a pilot study, development of flip charts for use in talking with the women, and ongoing evaluation of the informed consent process.

Our preliminary focus groups suggested women may wish to defer receipt of test results until after delivery. As a result, we added check boxes to the informed consent form that allow women to be tested and treated in labor; but to receive post-test counseling after delivery.

Prior to enrolling participants in the MIRIAD project, we did a pilot study of informed consent procedures. We conducted a "mock" informed consent process for MIRIAD with 8-10 known HIV-infected women and 8-10 HIV-uninfected women in labor. We developed a series of open-ended questions for potential participants. We then looked at the subjective reaction to the informed consent process, e.g.: *Is there anything you did not like? Are there situations that would have prevented you from participating?* We also assessed participants' comprehension of the risks, benefits, and purpose of participating in the project. Finally, we did an evaluation of pain and pain medication in the labor and delivery process.

A third approach involved the development of small flip charts containing pictures with accompanying text to be used with women in labor. These flip charts were piloted with focus groups.

Finally, we are conducting an ongoing evaluation of the informed consent process in MIRIAD. We are conducting postpartum interviews of women who accepted testing (both those found to be HIV-positive and those found to be HIV-negative) and of women who declined to be tested. Questions deal with the woman's reasons for declining or accepting the test and her comprehension of the process and its purpose.

In summary, there are major challenges in offering rapid HIV counseling and testing in labor to a particularly vulnerable group of women at a particularly vulnerable time. A major aim of MIRIAD is to find out how to best approach these women.

Update on HIV Rapid Tests

Bernard M. Branson, Division of HIV/AIDS Prevention–Surveillance and Epidemiology, Centers for Disease Control and Prevention

Since August 1999 New York State has required expedited HIV testing of pregnant women in labor or their newborns if no intra-pregnancy test result was available. Data presented at the 8th Conference on Retroviruses and Opportunistic Infections for the period October 1, 1999 to June 30, 2000 indicated that

69 mother-infant pairs in New York State had a positive expedited test: 41 true-positives as determined by EIA/Western Blot and 28 false-positives. SUDS was the initial test for 25 mothers and 11 infants; EIA was the initial test for 23 mothers and 10 infants. The reactive SUDS was confirmed in 10 mothers and 5 infants, yielding a positive predictive value for SUDS of 42%. The reactive EIA was confirmed in 18 mothers and 8 infants, yielding a positive predictive value for EIA of 79%. Four mothers and one infant had a reactive SUDS followed by a reactive EIA. All of these were confirmed, for a positive predictive value of 100% for a reactive SUDS followed by a reactive EIA.

An unexpected outcome of the new expedited testing regulations has been that HIV testing during the prenatal period has increased from 60% to 90% of all mothers in New York state since the inception of the regulations.

CDC is engaged in several efforts to increase the availability of rapid tests. It is encouraging manufacturers to commercialize rapid tests in the United States. It conducts clinical trials to establish test performance in settings of intended use. It is also evaluating the use of specific combinations of rapid tests to increase predictive value. Finally it has a "Treatment IDE" for expanded access to rapid tests.

Many candidate rapid HIV tests can use serum, whole blood, or plasma. Results can be read in 10 to 20 minutes. Sensitivities and specificities of the tests are extremely high. In one performance test with repository sera (196 HIV+, 200 HIV-), sensitivity ranged from 97.9% to 100% and specificity ranged from 94.5% to 99.5% for the five commercial tests included. In another performance test with repository sera (206 HIV+, 194 HIV-), sensitivity ranged from 99% to 100% and specificity ranged from 98.9% to 100% for the four commercial tests included.

Performance results of four commercial rapid tests using whole blood (prospective, 341HIV+, 466 HIV- venipuncture specimens) yielded sensitivities ranging from 95.3% to 100% and specificities from 99.3% to 100%. Performance results of six commercial tests using plasma (341 HIV+, 466 HIV- persons) yielded sensitivities ranging from 96.7% to 100% and specificities from 98.5% to 100%.

Application can be made to FDA for an investigational device exemption (IDE) for products or "treatments" not yet approved. This IDE allows use of investigational tests in certain populations and situations. It requires an investigator, a protocol, and IRB approval. Manufacturers would normally request an IDE to evaluate a single test. However, under this exemption, CDC is looking at the performance of several tests in combination.

Discussion Summary

A participant asked if New Orleans was doing any point-of-care rapid HIV testing on Labor & Delivery wards. Ms. Foxworth replied that currently all HIV testing was being done in the laboratory, but that with the initiation of the MIRIAD study they were hoping to begin point-of-care testing with L&D nurses doing the testing.

A participant pointed out that the programs presented by New Orleans and New Haven were conducted in large hospitals with extensive laboratory facilities. These rapid testing strategies might be even more useful in a setting where large labs are not available, although the implementation of such programs might be more difficult in these settings.

In response to several questions, Dr. Branson clarified that a treatment investigational device exemption (IDE) is submitted by a manufacturer to the FDA for a single rapid test and that at least one, if not more, treatment IDEs were likely to be approved in the near future (i.e., 6 weeks). If approved, in order to use the rapid test, an institution would need to apply for use. This application would require a principle investigator overseeing the program, a protocol, and IRB approval from the site. It is unclear how cumbersome this process would be for the sites. The manufacturer might provide a web site to enroll the principle investigator and a common protocol. This would simplify the process. Dr. Branson also clarified that these tests, if granted a treatment IDE, would not be FDA-approved. Rather, the treatment IDE is a way to have access to an investigational device to diagnose or treat a serious condition in cases where nothing else is available (in this case there is no FDA-approved rapid test currently available).

A participant asked if the information learned from the informed consent process in MIRIAD would be applicable to non-research settings. Dr. Jamieson responded that this was the intent of the evaluation component of the informed consent process in MIRIAD and that the investigators hoped that the information would be widely generalizable. Dr. Smith (NIDA, NIH) raised concerns about leaving the determination of whether or not women were competent/able to provide informed consent in labor up to individual providers; another participant concurred. She suggested instead providing objective criteria for who could be approached for the study. Dr. Jamieson felt that it would be difficult to determine a priori what factors would render a woman incompetent. For example, one might hypothesize that the administration of narcotic intravenous medication (e.g. IV fentanyl) would make a woman less able to comprehend the informed consent process. Alternatively, administration of a low-dose short-acting narcotic medication to relieve pain might make a woman feel more in control and better able to comprehend what is being presented.

A participant stressed the importance of partner counseling for women identified as HIV-positive through rapid testing.

Dr. Smith raised the issue that many potential participants might be accessing care at multiple sites and at different times during their pregnancy (triage, emergency rooms, alternate care settings) even though they are not registered for prenatal care. She suggested that MIRIAD collect information on this. She further stated that it was important not to ignore/disregard the community and context within which these women were living. In addition, it was important to keep in mind how this research study would be perceived in the larger non-medical community. The MIRIAD representatives all agreed that these were excellent points.